

Supplemental material

Table S1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2-3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2-3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3-4, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3-4; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4; Supplementary Tables S2-S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4-7; Figures 2-5, Supplementary Figures S1, S2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-6; Figures 2-5, Supplementary Figures S1, S2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Tables S2-S6, Figures S3-S8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	4-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	4, 7-9; Supplementary Tables S7, S8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

Table S2. Risk of bias assessment of randomized controlled trials included in the meta-analysis of serum total cholesterol and low-density lipoprotein levels using the revised tool for assessing risk of bias in randomized trials (Rob 2).

Study	D1	D2	D3	D4	D5	Overall
Ahuja and Ball, 2006						
Arent et al., 2018						
Cha et al., 2013						
Kim et al., 2010						
Lim et al., 2015						
Qin et al., 2017						
Taghizadeh et al., 2017						
Urbina et al., 2017						
Yuan et al., 2015						

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low

According to the Rob 2 tool in case of serum total cholesterol and low-density lipoprotein levels, 6 studies are considered overall as high risk (Ahuja and Ball 2006, Arent et al. 2018, Cha et al. 2013, Kim et al. 2010, Lim et al. 2015, Urbina et al. 2017), 1 study as raising some concerns (Qin et al. 2017), and 2 studies as low risk (Yuan et al. 2016, Taghizadeh et al. 2017).

Table S3. Risk of bias assessment of randomized controlled trials included in the meta-analysis of serum triglyceride and high-density lipoprotein levels using the revised tool for assessing risk of bias in randomized trials (Rob 2).

Study	D1	D2	D3	D4	D5	Overall
Ahuja and Ball, 2006						
Arent et al., 2018						
Cha et al., 2013						
Lim et al., 2015						
Qin et al., 2017						
Taghizadeh et al., 2017						
Urbina et al., 2017						
Yuan et al., 2015						

Domains:

- D1: Bias arising from the randomization process.
- D2: Bias due to deviations from intended intervention.
- D3: Bias due to missing outcome data.
- D4: Bias in measurement of the outcome.
- D5: Bias in selection of the reported result.

Judgement

- High
- Some concerns
- Low

According to the Rob 2 tool in case of serum triglyceride and high-density lipoprotein levels, 5 studies are considered overall as high risk (Ahuja and Ball 2006, Arent et al. 2018, Cha et al. 2013, Lim et al. 2015, Urbina et al. 2017), 1 study as raising some concerns (Qin et al. 2017), and 2 studies as low risk (Yuan et al. 2016, Taghizadeh et al. 2017).

Table S4. Risk of bias assessment of randomized controlled trials included in the meta-analysis of fasting plasma glucose levels using the revised tool for assessing risk of bias in randomized trials (Rob 2).

Study	D1	D2	D3	D4	D5	Overall
Arent et al., 2018						
Qin et al., 2017						
Taghizadeh et al., 2017						
Urbina et al., 2017						
Yuan et al., 2015						

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low

According to the Rob 2 tool in case of fasting plasma glucose levels, 2 studies are considered overall as high risk (Arent et al. 2018, Urbina et al. 2017), 1 study as raising some concerns (Qin et al. 2017), and 2 studies as low risk (Yuan et al. 2016, Taghizadeh et al. 2017).

Table S5. Risk of bias assessment of randomized controlled trials included in the meta-analysis of fasting plasma insulin levels using the revised tool for assessing risk of bias in randomized trials (Rob 2).

	D1	D2	D3	D4	D5	Overall
Ahuja and Ball, 2006						
Taghizadeh et al., 2017						
Urbina et al., 2017						
Yuan et al., 2015						

Domains:

- D1: Bias arising from the randomization process.
- D2: Bias due to deviations from intended intervention.
- D3: Bias due to missing outcome data.
- D4: Bias in measurement of the outcome.
- D5: Bias in selection of the reported result.

Judgement

-  High
-  Some concerns
-  Low

According to the Rob 2 tool in case of fasting plasma insulin levels, 2 studies are considered overall as high risk (Ahuja and Ball 2006, Urbina et al. 2017), and 2 studies as low risk (Yuan et al. 2016, Taghizadeh et al. 2017).

Table S6. Risk of bias assessment of a non-randomized crossover trial included in the meta-analysis using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Kang et al., 2016								

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
 Moderate
 Low

According to the ROBINS-I tool, the overall quality of the study by Kang et al. (2016) is considered as moderate.

Table S7. Summary of findings using the GRADE approach.

Analyzed blood parameter	Capsaicinoid - placebo SMD (95% CI)	Number of subjects (and studies)	Quality of the evidence
Total cholesterol	-0.52 (-0.83, -0.21)	398 (10)	⊕⊕, Low because of risk of bias and imprecision
LDL	-0.30 (-0.57, -0.02)	398 (10)	⊕⊕, Low because of risk of bias and imprecision
Triglyceride	-0.39 (-1.15, 0.37)	370 (9)	⊕⊕, Low because of inconsistency and imprecision
HDL	-0.03 (-0.37, 0.32)	370 (9)	⊕⊕, Low because of imprecision and inconsistency
Fasting glucose	0.41 (-0.26, 1.07)	213 (5)	⊕, Very low because of imprecision and inconsistency
Fasting insulin	0.28 (-0.25, 0.82)	166 (4)	⊕, Very low because of imprecision and inconsistency

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMD, standardized mean difference.

Table S8. Quality of the evidence for all analyzed outcomes using the GRADE the approach.

Measured outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Quality of evidence
Total cholesterol	Most studies were RCTs (starts as high quality)	High risk of bias in most analyzed studies (-1)	9 out of 10 studies involved healthy individuals; heterogeneity was moderate mainly due to one study (0)	The interventions contained capsaicinoids as defined in our PICO (0)	Wide CIs often crossing the null value (-1)	Some asymmetry in funnel plot (0)	None	Low ●●○○
LDL	Most studies were RCTs (starts as high quality)	High risk of bias in most analyzed studies (-1)	9 out of 10 studies involved healthy individuals; heterogeneity was moderate mainly due to one study (0)	The interventions contained capsaicinoids as defined in our PICO (0)	Wide CIs often crossing the null value (-1)	Some asymmetry in funnel plot (0)	None	Low ●●○○
Triglyceride	Most studies were RCTs (starts as high quality)	High risk of bias in most analyzed studies (-1)	8 out of 9 studies involved healthy individuals; heterogeneity was high mainly due to one study (0)	The interventions contained capsaicinoids as defined in our PICO (0)	Wide CIs often crossing the null value (-1)	Some asymmetry in funnel plot (0)	None	Low ●●○○
HDL	Most studies were RCTs (starts as high quality)	High risk of bias in most analyzed studies (-1)	8 out of 9 studies involved healthy individuals; heterogeneity was high mainly due to one study (0)	The interventions contained capsaicinoids as defined in our PICO (0)	Wide CIs often crossing the null value (-1)	Some asymmetry in funnel plot (0)	None	Low ●●○○
Fasting glucose	Most studies were RCTs (starts as high quality)	High risk of bias in most analyzed studies (-1)	1 out of 5 studies involved women with gestational diabetes; high heterogeneity (-1)	The interventions contained capsaicinoids as defined in our PICO (0)	Wide CIs often crossing the null value; low number of studies (-2)	Some asymmetry in funnel plot (0)	None	Very low ●○○○
Fasting insulin	Most studies were RCTs (starts as high quality)	High risk of bias in most analyzed studies (-1)	1 out of 4 studies involved women with gestational diabetes; high heterogeneity (-1)	The interventions contained capsaicinoids as defined in our PICO (0)	Wide CIs often crossing the null value; low number of studies (-2)	Some asymmetry in funnel plot (0)	None	Very low ●○○○

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PICO, Patients, Intervention, Comparison, Outcome model; RCT, randomized controlled trial.

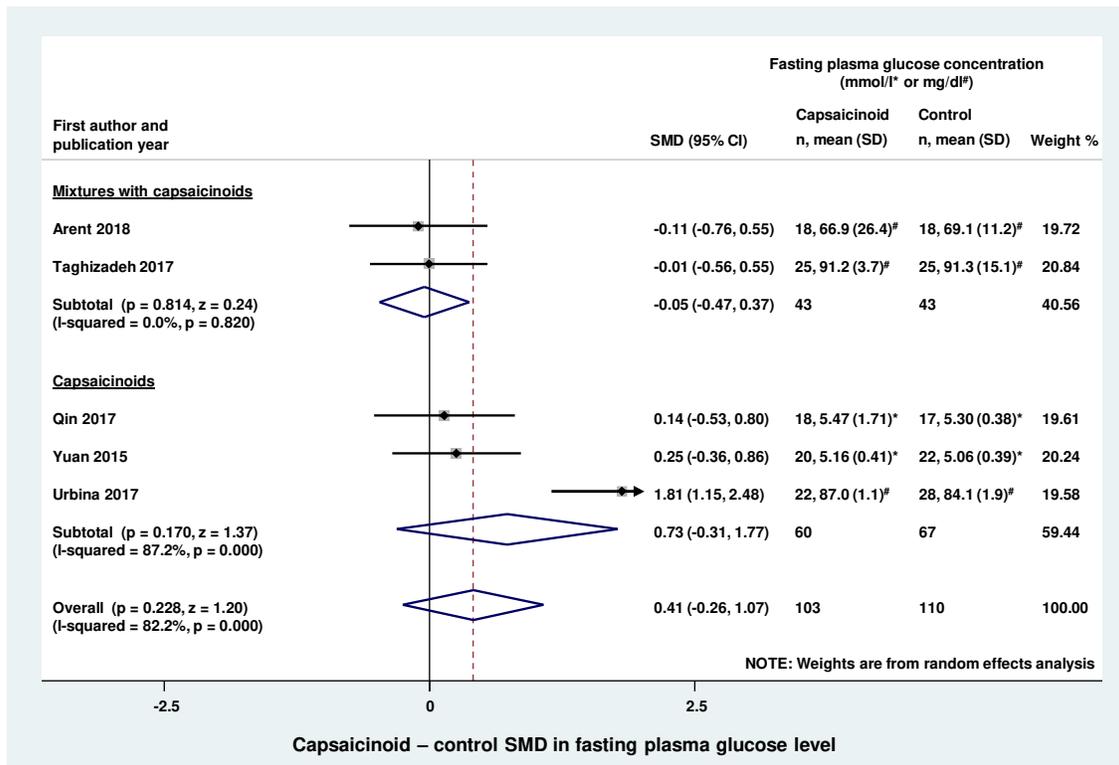


Figure S1. Forest plot of the effects of capsaicinoid-containing mixtures (top) and capsaicinoids (bottom) on fasting plasma glucose level. There was no significant difference between the two subgroups ($Q = 1.846$; $p = 0.174$). CI, confidence interval; SD, standard deviation; SMD, standardized mean difference.

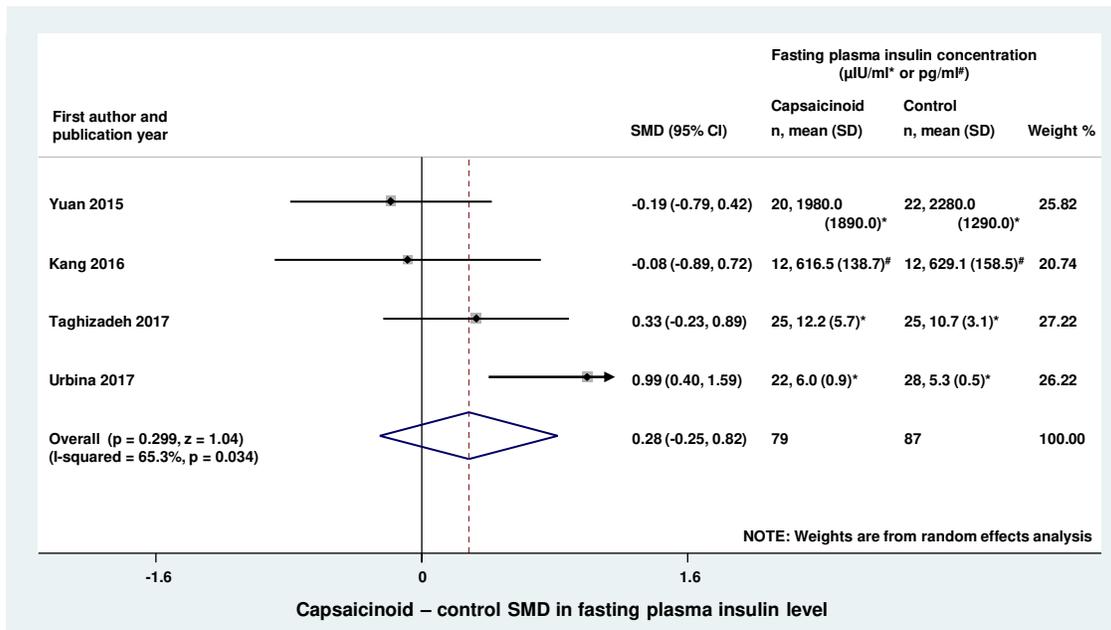


Figure S2. Forest plot of the effects of capsaicinoids (Kang et al. 2016, Urbina et al. 2017, Yuan et al. 2015) and capsaicinoid-containing mixtures (Taghizadeh et al. 2017) on fasting plasma insulin level. CI, confidence interval; IU, international unit; SD, standard deviation; SMD, standardized mean difference.

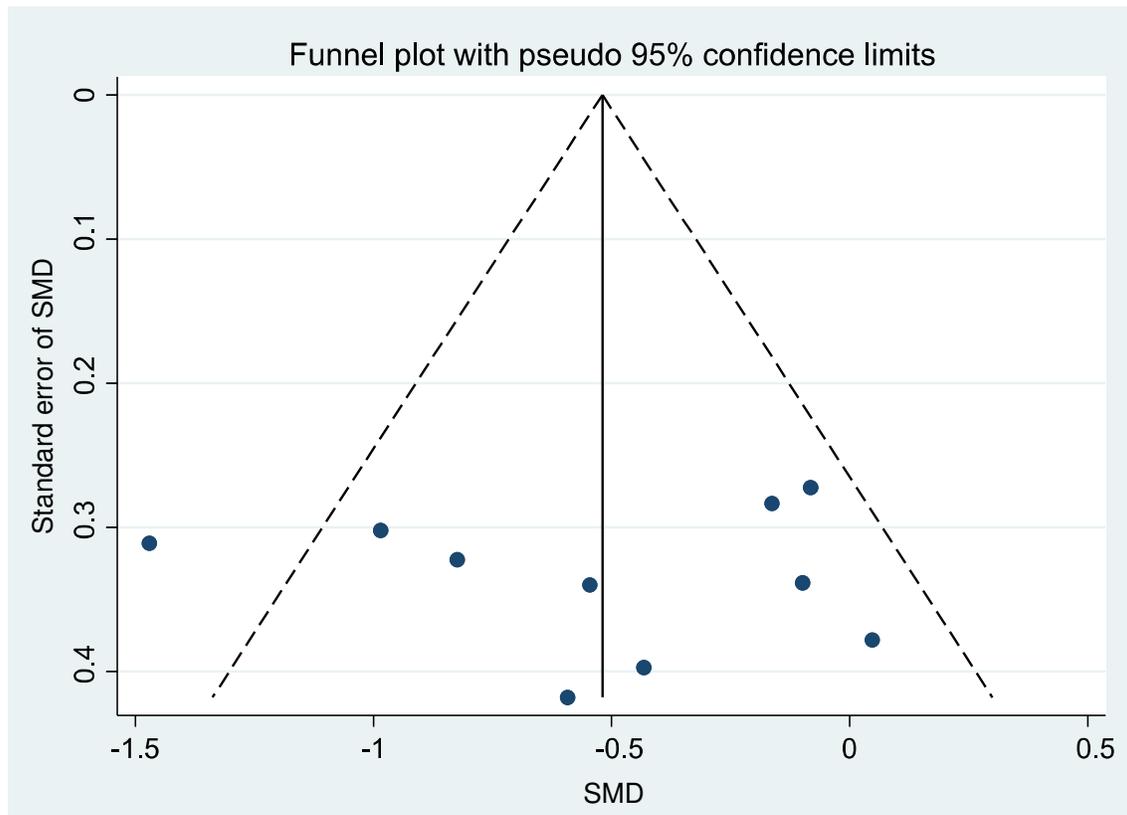


Figure S3. Funnel plot of the studies that were included in the forest plot of the standardized mean differences (SMDs) for serum total cholesterol level in the capsaicinoid-treated and the control groups (Figure 2) (Egger's test $p = 0.973$).

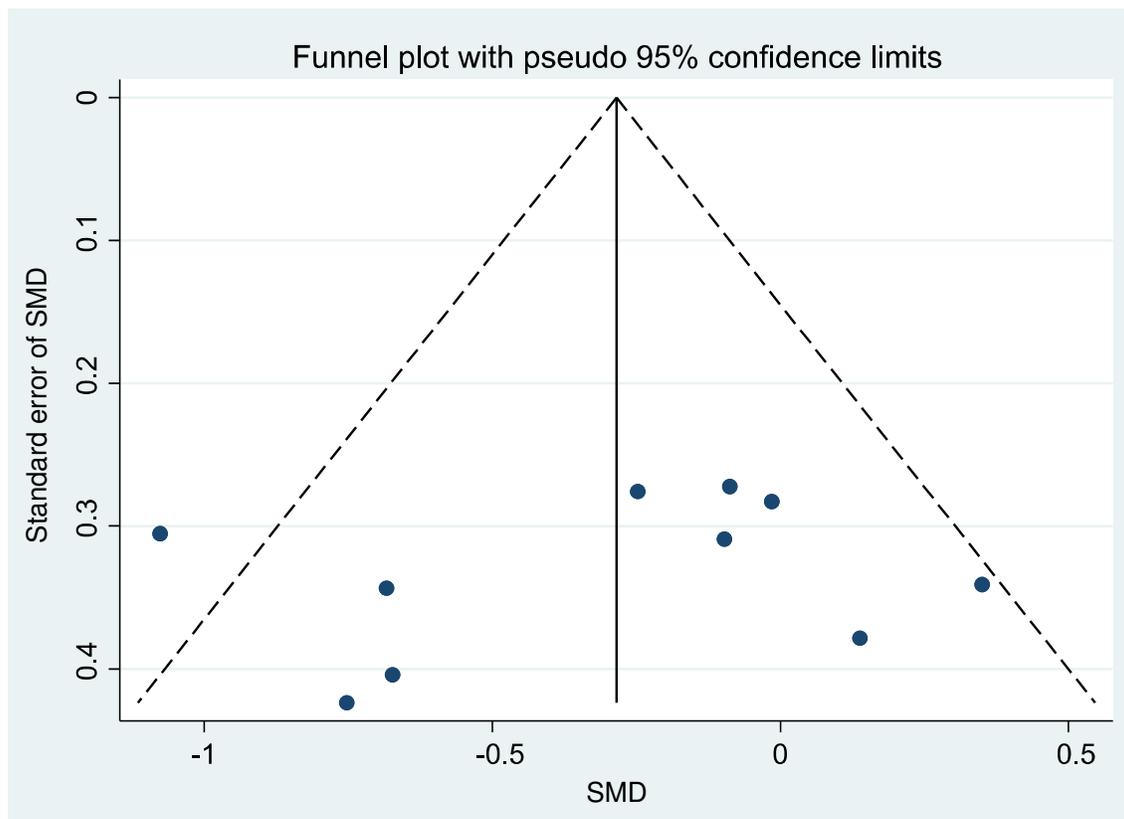


Figure S4. Funnel plot of the studies that were included in the forest plot of the standardized mean differences (SMDs) for serum low-density lipoprotein level in the capsaicinoid-treated and the control groups (Figure 3) (Egger’s test $p = 0.523$).

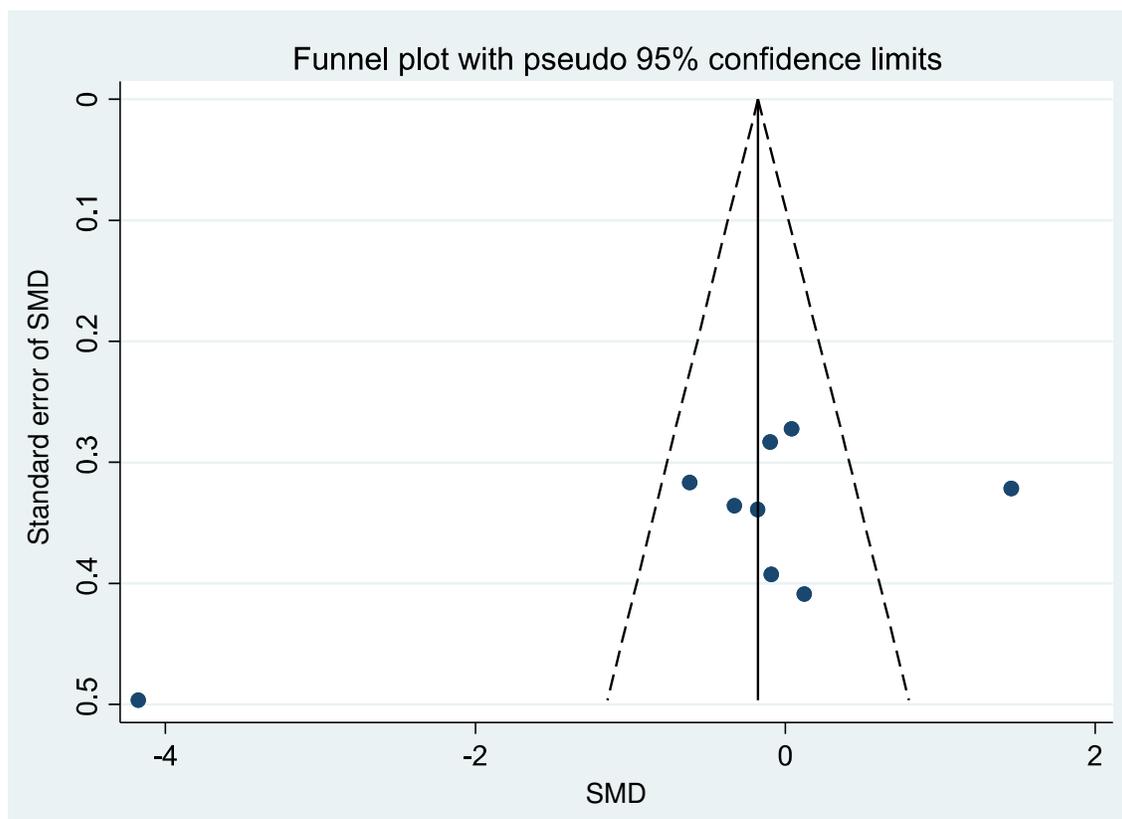


Figure S5. Funnel plot of the studies that were included in the forest plot of the standardized mean differences (SMDs) for serum triglyceride level in the capsaicinoid-treated and the control groups (Figure 4).

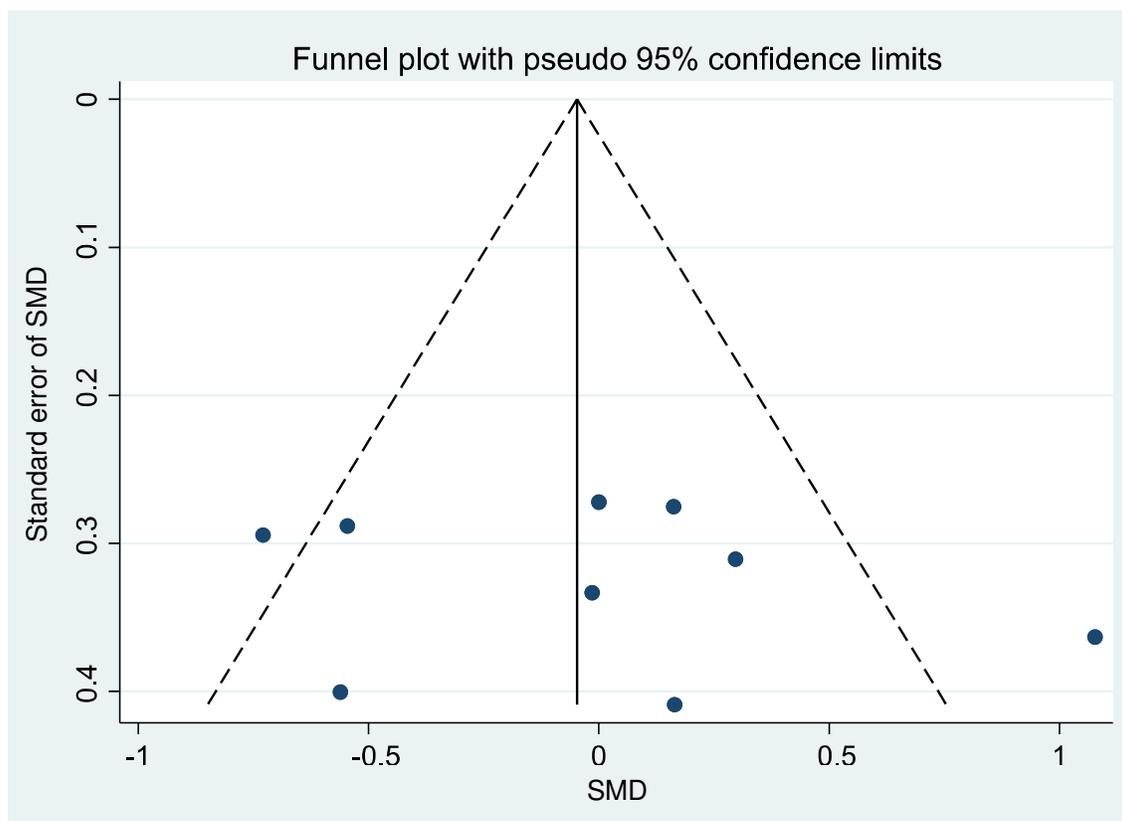


Figure S6. Funnel plot of the studies that were included in the forest plot of the standardized mean differences (SMDs) for serum high-density lipoprotein level in the capsaicinoid-treated and the control groups (Figure 5).

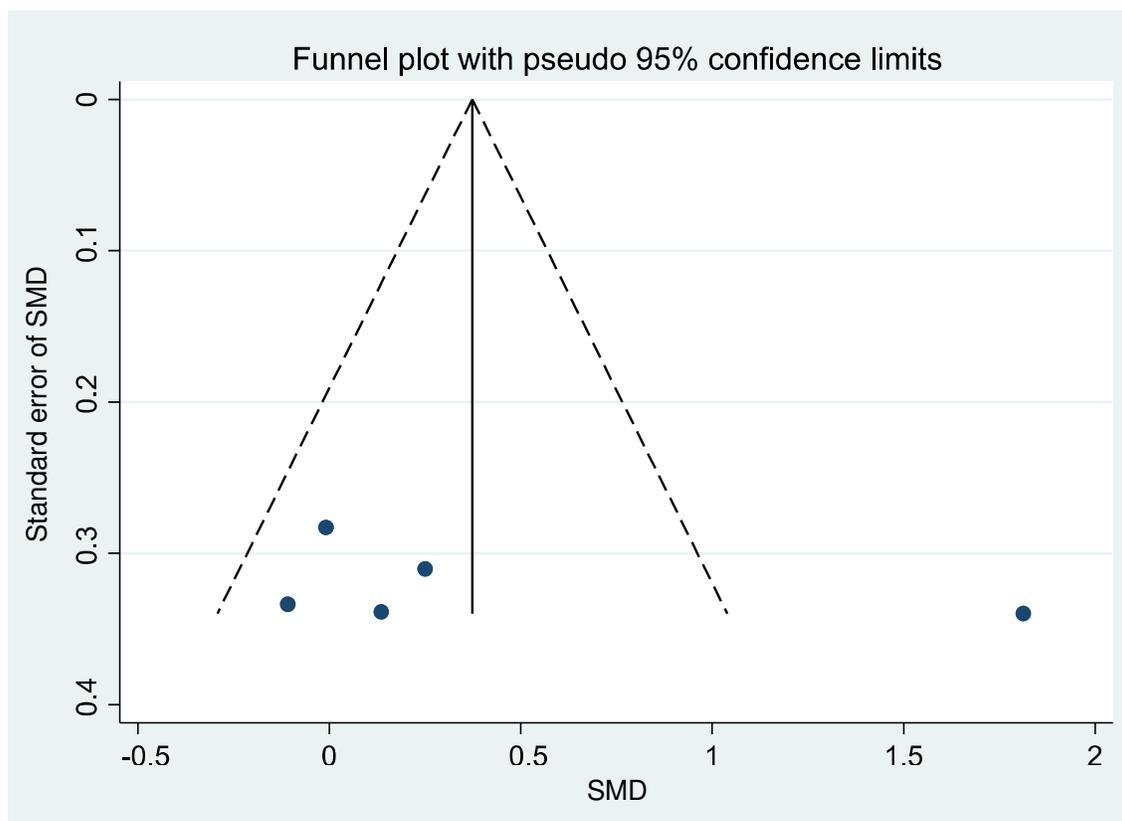


Figure S7. Funnel plot of the studies that were included in the forest plot of the standardized mean differences (SMDs) for fasting plasma glucose level in the capsaicinoid-treated and the control groups (Supplementary Figure S1).

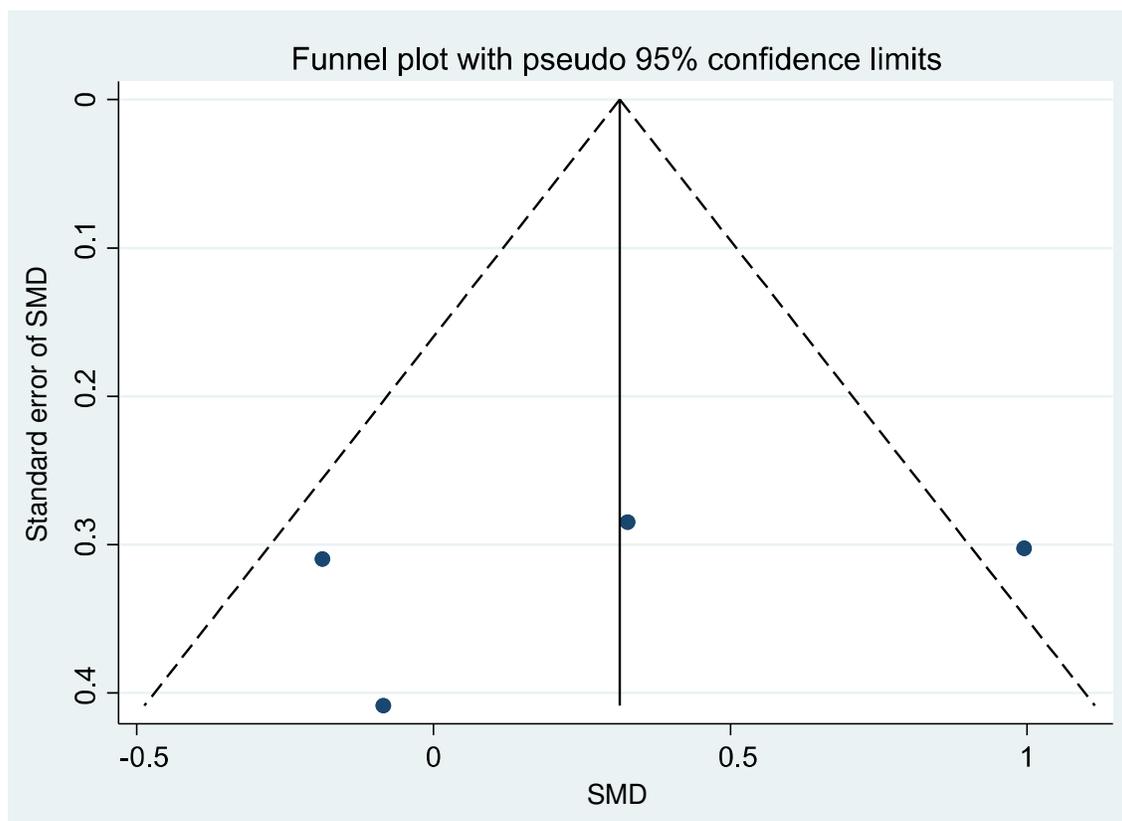


Figure S8. Funnel plot of the studies that were included in the forest plot of the standardized mean differences (SMDs) for fasting plasma insulin level in the capsaicinoid-treated and the control groups (Supplementary Figure S2).